REMARKS

The claims have been amended so as to define the invention in terms of the flat substrate microarrays that are expected to present the primary environment of commercial interest. Support in the specification for additions to claim 1 is found as set forth hereinafter. Reference is made to solid flat plates at page 20, line 15. As set forth in the paragraph on page 22 between lines 7 and 14, the individual three-dimensional cells protrude from the flat surface and provide a significant increase in the quantity of binding entities that can be immobilized therein, as compared to a two-dimensional array. Support for the covalent linkage of the binding entities, either directly or through an intermediate agent, with the reactive isocyanate groups of the hydrogel is found in original claim 6 and claim 10. Support for the lower limit of about 5% of the active isocyanate groups in the prepolymer, that was added to claim 7, is found at page 13, lines 15-21.

The additions to independent claims 18 and 31 are similarly supported by those portions of the specification mentioned above. The addition to claim 35 to add aptamers as additional binding agents for the capture of proteins is found at page 15, lines 25-28.

Support for the changes to independent claim 41 is likewise found at those locations specified with respect to claim 1. The polymers employed are, of course, urethane polymers as set forth at page 10, lines 15-23, and the prepolymers have sufficient quantities of active isocyanates so as to provide a hydrogel that is isocyanate functional after crosslinking takes place to form the polyurea-urethane hydrogel (page 10, line 23). Such enables covalent linkage to the binding entities. Support for the specific

amount of excess polyisocyanate in the prepolymer that forms the urethane-based polymer, which is added to claim 42, is found at page 11, line 10.

New claim 46 is patterned after claim 1 but recites that up to about 5% of its isocyanate groups are covalently bound to the derivatized groups of the substrate, which finds support at page 18, lines 10-12. The subsequent percentage range finds support at page 13, lines 20-21.

The invention, as defined in independent claims 1 and 31, would not be obvious from the disclosure of U.S. Patent No. 5,624,711 to Sundberg et al. (hereinafter Sundberg et al.) in combination with the disclosure of U.S. Patent No. 5,169,720 to Braatz et al.

Applicant does not dispute (1) that Sundberg et al. discloses derivatized supports, e.g. a glass slide having a flat surface treated with an aminoalkyltrialkoxysilane, on which syntheses subsequently take place (see column 11, lines 20-27 and 66-67), or (2) that following such syntheses, the plate will have an array of ligands. The important difference between the Sundberg et al. disclosure and Applicants' invention is how those ligands are attached to the plate for presentation to targets in an aqueous solution so as to facilitate hybridization between targets of interest in solution and the ligands of that array.

Sundberg et al. do not employ a hydrogel; they coat the derivatized plate with a polymer from a class of resins designed for solid-phase synthesis, i.e. a polymeric resin such as one commercially sold for solid-phase peptide synthesis (see column 13, lines 46-49), e.g. a chloromethylated styrene-divinylbenzene (Merrifield resin) or a PAM resin (column 14, lines 25-27). These resins are well-known throughout the field of solid-phase peptide synthesis, and they have been used for this purpose for over 20 years.

The suggested application of this polymeric resin is by dip-coating, see column 15, lines 35-52. The result is a polymer-coated surface wherein the polymer layer is uniform in thickness (see column 16, lines 51-52), e.g. a thin film of polymer on a glass support (column 25, lines 23-24). This uniform, thin film is of substantially monomolecular thickness (see FIG. 1). The chosen resin provides functional amino sites at which solid-phase synthesis of ligands can begin. The ligands are then synthesized *in situ*, as by sequentially adding individual amino acids to build peptides, for example as depicted in FIG. 17. The result is clearly a two-dimensional array of individual molecules attached to the coated surface of the plate.

In summary, Sundberg et al. advocate the application of a thin uniform polymer of a Merrifield resin or the like which serves as a base for the solid-phase syntheses of peptide or oligonucleotide ligands at discrete patches to create an array. The result is a two-dimensional array; the surface is uniform, with only the synthesized ligand molecules extending from the surface at such discrete locations. The group of ligands are directly attached to the flat surface, and the group is only one molecule thick. Thus, the Sundberg et al. product (which uses a solid-phase synthesis resin) is not a microarray having a flat surface from which individual three-dimensional cells protrude at discrete locations, with each cell having a thickness of at least about 20 microns. There are no such 3D cells; they employ individual 2D patches which are 1 molecule thick.

The Examiner would propose to substitute the polymer taught in Braatz et al. for the thin, uniform Merrifield resin coating taught by Sundberg et al. However, this is clearly a combination born in hindsight, as the purpose and the disclosure of Braatz et al. teaches directly away from the purpose of the Sundberg et al. thin uniform polymeric

resin coating. Sundberg et al. teach the *in situ* building of a microarray by synthesis of oligomers at discrete locations on that surface (see title). To carry out such solid-phase synthesis, they require a polymeric resin, such as a Merrifield resin or a PAM resin, which will serve as the base upon which the solid-phase syntheses can be initiated (see Example 6 beginning at column 24, line 37). Braatz et al. are concerned with the creation of a polyurea-urethane polymer that is protein non-adsorptive, i.e. it is resistant to protein adsorption. Therefore, not only do Braatz et al. likewise teach preparing "a coating in the form of a thin film or a monomolecular or substantially monomolecular layer" (column 9, lines 29-30), i.e. a uniform thin film like Sundberg et al. advocate using, but they teach a coating that is protein non-adsorptive. Such is clearly not a coating that one would consider using as a base for synthesizing peptides or proteins *in situ* to create an array, nor is it one that would be effective.

As pointed out at column 10, lines 12-14 of Braatz et al., the surface coated with the prepolymer is contacted with water, preferably by immersion in a water bath. Immersion is preferably for a very substantial period, e.g. 17 hours (see column 17, lines 9-12). This step crosslinks the uniform layer of prepolymer by forming urea linkages and eliminates any residual reactive isocyanate groups; thus, it creates a coated substrate that would not be useful in the Sundberg et al. procedure. In fact, it is the antithesis of what Sundberg requires, i.e. a polymeric resin that has highly reactive groups for the initiation of synthesis of oligomers -- because Braatz et al. specifically eliminate any residual isocyanate groups (col. 9, lines 5-7). It is likewise the antithesis of Applicants' claimed product which relies upon the isocyanate groups of the hydrogel to covalently link either to the binding entities or to intermediate agents. Thus, in addition to failing to teach other

than just another thin film coating procedure, Braatz et al. do not teach a polymer that would be fairly substitutable for the polymeric solid phase synthesis resins used by Sundberg et al. Moreover, the Braatz et al. surface coating should have sufficient integrity to allow the coated item, e.g. tubing, catheter, labware, filler, etc. to be handled; in contrast, Applicants' 3D cells formed from microdroplets are minute spots on a supportive flat surface that consist of an elastic gel that is primarily water.

For essentially the same reasons as set forth above, the combination of U.S. Patent No. 6,406,921 to Wagner et al. (hereinafter Wagner et al.) in view of the disclosure of Braatz et al. likewise fails to render the claimed invention obvious; both references teach the application of thin, uniform layers to a substrate. Applicants do not dispute that Wagner et al. teach the creation of a peptide array on a flat silicon wafer or the like, but they likewise create a two-dimensional array using a monomolecular layer as the coating on the substrate. They specifically call their array a "two-dimensional array" (see column 9, lines 49-50; column 17, lines 2-3; and Examples 1 and 2 in column 21). The coating material is likewise referred to throughout the description as a "monolayer"; for example, the molecules that may create the monolayer are discussed throughout column 19. Evidence of this is also found, in Example 4, where the monolayer is deposited by immersion in a 1 millimolar (mM) solution of DSU in chloroform which is thereafter rinsed with ten volumes of solvent; the layer resulting from immersion in such a dilute concentration would be essentially one molecule or so thick. All this is consistent with the reference to the array as being a 2D-protein Array (Example 6), or a two-dimensional Array (Example 7) (see subtitles).

With respect to its asserted combination with Braatz et al., the prior discussion is equally pertinent; when one is interested in a coating that is going to provide a base to which previously synthesized proteins can be linked in discrete patches, one is not going to look to the "protein non-adsorptive" coatings taught by Braatz et al. Thus, for the reasons set forth above, Braatz et al., in this respect, also teach away from the objective of Wagner et al., namely, to provide a coating to which proteins can be linked so as to create a two-dimensional array.

With particular respect to Applicants' claims, attention is called to the recitations set forth hereinafter with respect to independent claims 1, 18, 31, 41, and 46.

Claim 1 defines the biochip as comprising a solid substrate with a flat top surface to which are attached a plurality of individual three-dimensional hydrogel cells, each at least 20 microns thick, at discrete locations to form an array of discrete individual three-dimensional cells protruding from the otherwise flat surface, which hydrogel cells are formed from an isocyanate-functional prepolymer with urethane linkages. The claim further recites that different binding entities are immobilized within or upon the various hydrogel cells via covalent linkage directly or indirectly to reactive isocyanate groups.

Claim 18 similarly recites a hydrogel biochip where the flat top surface of the substrate has a plurality of individual three-dimensional hydrogel cells bound thereto and protruding therefrom at discrete locations to form an array, each being at least 20 micron thick, with intermediate agents immobilized within or upon the hydrogel by covalent binding to reactive isocyanate groups of the hydrogel and with different protein binding entities bound to the intermediate agents so that said protein binding entities can assume their native confirmations.

Claim 31 similarly recites a biochip having a substrate with a flat top surface to which there are bound a plurality of individual, three-dimensional hydrogel cells which protrude upward therefrom, each at least about 20 microns thick and disposed at discrete locations to form an array, with different protein binding entities being immobilized via linkage to isocyanate groups of said hydrogel urethane polymer.

Claim 41 likewise recites a biochip on which a plurality of individual, three-dimensional hydrogel cells are bound to and protrude from a flat top surface, which individual hydrogel cells are at least 20 microns thick and comprise a urethane polymer formed of PEG, PPG or a copolymer thereof and polyisocyanates, wherein intermediate agents are immobilized within or upon said hydrogel cells via reaction with isocyanate groups of said hydrogel and different binding entities are bound to these intermediate agents by interaction therewith so they can assume their native configuration.

Claim 46 defines the biochip as comprising a solid substrate with a derivatized flat top surface from which a plurality of individual three-dimensional hydrogel cells, each at least 20 microns thick, protrude at discrete locations to form an array. The hydrogel cells are formed from an isocyanate-functional urethane prepolymer with up to about 5% of the isocyanate groups covalently bound to the derivatized surface. The claim further recites that different binding entities are immobilized within or upon the various hydrogel cells via covalent linkage directly or indirectly to between about 5% to 15% of the reactive isocyanate groups of the prepolymer.

In summary, Sundberg et al. teach a thin, uniform coating of a resin material suitable for solid-phase peptide synthesis (such as a Merrifield resin or a PAM resin) on which an array is formed by *in situ* building of oligomers at discrete patches of the resin

surface; the result is a two-dimensional array created by the plurality of single length oligomers protruding from the surface at each location. The disclosure of Wagner et al. is similar. A solid flat surface is coated with a monolayer of a suitable polymer, e.g. DSU (see Example 4 thereof), by immersion into a very dilute, i.e. 1 millimolar, solution of DSU which would result in a layer of about 1 molecule thick; presynthesized proteins are attached to this layer in patches. The only items protruding from the surface are the single peptide molecules that are attached; the result is a two-dimensional array as it is properly termed throughout the patent.

The combination of either such two-dimensional array reference that does not use a hydrogel with the disclosure of Braatz et al. is one born only in hindsight. There is likewise nothing three-dimensional about the uniform Braatz et al. coating, and its disclosure teaches away from the objective of either primary reference. It is likewise applied as a uniform, thin coating, and nothing in its disclosure would suggest the creation of three-dimensional cells of at least twenty micron thickness protruding from a flat surface. Moreover, no one would be inclined to substitute the polymer of Braatz et al. either for the solid-phase synthesis resin of Sundberg et al. or for the protein-attractive resin of Wagner et al. As its title states, the Braatz et al. polymer is "PROTEIN NON-ADSORPTIVE"; one wishing to create a protein array or the like on a flat surface would certainly not look to a polymer that is created for the simple purpose of not adsorbing proteins. It is respectfully requested that the rejection of independent claims 1, 18, 31 and 41, based upon the combination of the disclosures of either of the primary references with Braatz et al. be reconsidered and withdrawn.

In view of the foregoing, it is submitted that, in the absence of more pertinent prior art, independent claims 1, 18, 31, 41 and 46, and the claims dependent thereon, namely claims 3, 5-7, 9, 10, 17, 32-35, 42 and 43 should be allowed, along with presently withdrawn claims to nonelected species, namely claims 8, 11-14, 36 and 38-40. It was indicated that, upon allowance of the claims to the microarray, claims to a method of use, namely claims 44 and 45 would be rejoined and examined. These two claims are dependent upon claim 31 and thus include all of the recitations thereof; allowance of claims 44 and 45 following allowance of claim 31 is respectfully requested.

It is believed that this application should now be in condition for allowance, and favorable action is courteously solicited.

Respectfully submitted,

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